United States Patent Office

3,491,093

Patented Jan. 20, 1970

3,491,093

DERIVATIVES OF 5 AMINOMETHYL-4,5,6,7-TETRAHYDRO-4-OXOINDOLES

Irwin J. Pachter, Woodbury, and Karl Schoen, Kew Gardens, N.Y., assignors to Endo Laboratories Inc., Garden City, N.Y., a corporation of New York

No Drawing. Filed Nov. 29, 1967, Ser. No. 686,777

Int. Cl. C07c *27/56;* A61k *27/00*

U.S. Cl. 260—247.5 11 Claims

ABSTRACT OF THE DISCLOSURE

Novel N-substituted 5-aminomethyl-4,5,6,7-tetrahydro-4-oxoindoles and the acid addition salts thereof are prepared by the Mannich condensation of the desired 4,5,6,7-tetrahydro-4-oxoindoles with formaldehyde and the requisite amines.

These novel compounds have pharmacological activity as sedatives and tranquilizers.

RELATED APPLICATIONS

This application is a continuation-in-part of applicants' copending application Ser. No. 357,284, filed Apr. 3, 1964 now abandoned. Intermediates utilized in the preparation of the novel compounds of this invention are disclosed in our application Ser. No. 348,878, filed Mar. 2, 1964, now abandoned, and in continuation-in-part thereof, Ser. No. 549,135 filed May 11, 1966.

FIELD OF THE INVENTION

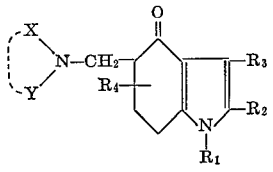
The present invention relates to novel compounds having psychopharmacological effects, in particular activity as antipsychotics.

DESCRIPTION OF THE PRIOR ART

Heretofore compounds of the N-substituted-5-aminomethyl-4,5,6,7-tetrahydro-4-oxoindole series have not been described.

SUMMARY

The compounds of the present invention have the following general structural formula



Formula A

and the acid addition salts thereof.

In Formula A, the substituents have the following significance:

R_1 designates hydrogen, a lower alkyl having a maximum of 4 carbon atoms, benzyl, phenyl or 2-, 3-, or 4-pyridyl;

R_2 and R_3 designate alkyl, alkenyl and cycloalkyl each having a maximum of 8 carbon atoms, phenyl, halogeno-phenyl or lower alkoxy phenyl;

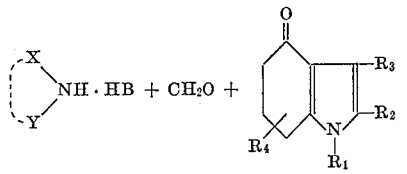
R_4 designates hydrogen or a lower alkyl having a maximum of 4 carbon atoms and being attached to carbon atom 6 or 7 of the indole nucleus;

X and Y designate lower alkyl, hydroxy lower alkyl, lower acyloxy alkyl, carbamoyloxy lower alkyl and phenyl lower alkyl;

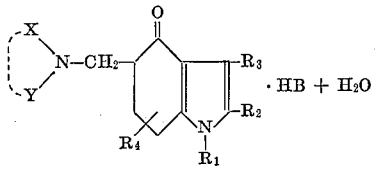
X and Y may be linked together and then constitute, together with a nitrogen atom, a heterocyclic ring having a maximum of 8 members.

A typical process for preparing the 5-aminomethyl-4,5,6,7-tetrahydro-4-oxoindoles of this invention is the

Mannich reaction, which can be illustrated by the following reaction scheme:



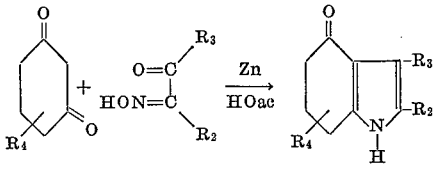
Formula I Formula II



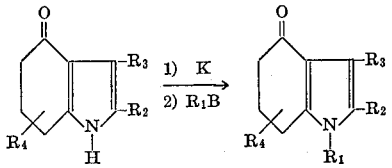
Formula A·HB

The most general method of preparing those intermediates is by the reduction of an α-oximinoketone in the presence of a cyclohexane-1,3-dione.

Condensation occurs during the reduction process to provide the final products.

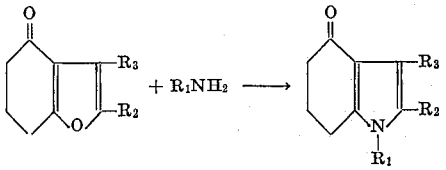


N-alkyl and N-benzyl intermediates may be prepared from the 4,5,6,7-tetrahydro-4-oxoindoles by treatment with an alkali metal which results in the formation of the alkali metal derivative, followed by the interaction of the alkali metal derivative with an N-alkylating or N-benzylating agent such as alkyl (or benzyl) halide or sulfate (R_1B(B designating the halogeno- or sulfato-moiety) to produce the desired product, as illustrated in the following reaction scheme:



Treatment with potassium metal affords a potassium derivative which then reacts with an alkyl halide or sulfate (R_1B) to produce the desired product.

As an alternate route to the synthesis of the 4,5,6,7-tetrahydro-4-oxoindole intermediates, one may use the method of H. Stetter and R. Lauterbach, Ann., 655, 20 (1962) in which ammonia or a primary amine is condensed with a derivative of 4,5,6,7-tetrahydro-4-oxobenzofuran.



In the preparation of the compounds of this invention by this method, an amine salt is generally used, although the corresponding free base can, at times, be employed.